Presentation 5 – Christopher Sinton

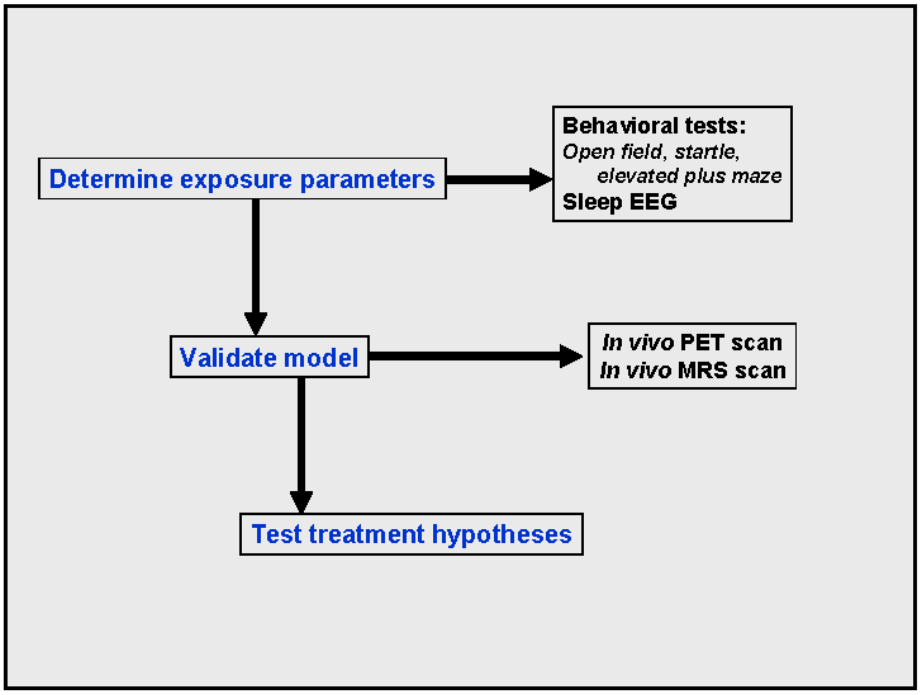
A rodent model of Gulf War Illness: development and validation

Does low-dose, repeated exposure to AChEi agents induce delayed minimal brain dysfunction?

Christopher M Sinton
Dept of Internal Medicine
UT Southwestern Medical Center

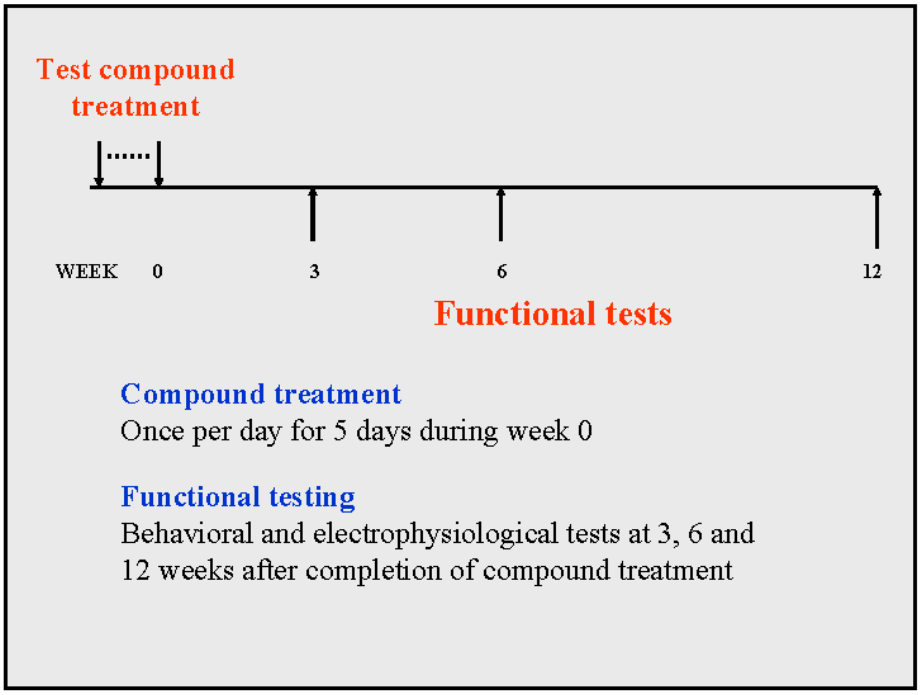
Principal goals of the study

- Establish the exposure parameters for AChEi agents that induce delayed CNS functional effects
- Examine the face validity of the model using non-invasive brain scans that can reproduce results found in GWI
- Determine the tests that are predictive of CNS functional effects
- Develop a platform against which mechanistic hypotheses and potential treatments can be tested



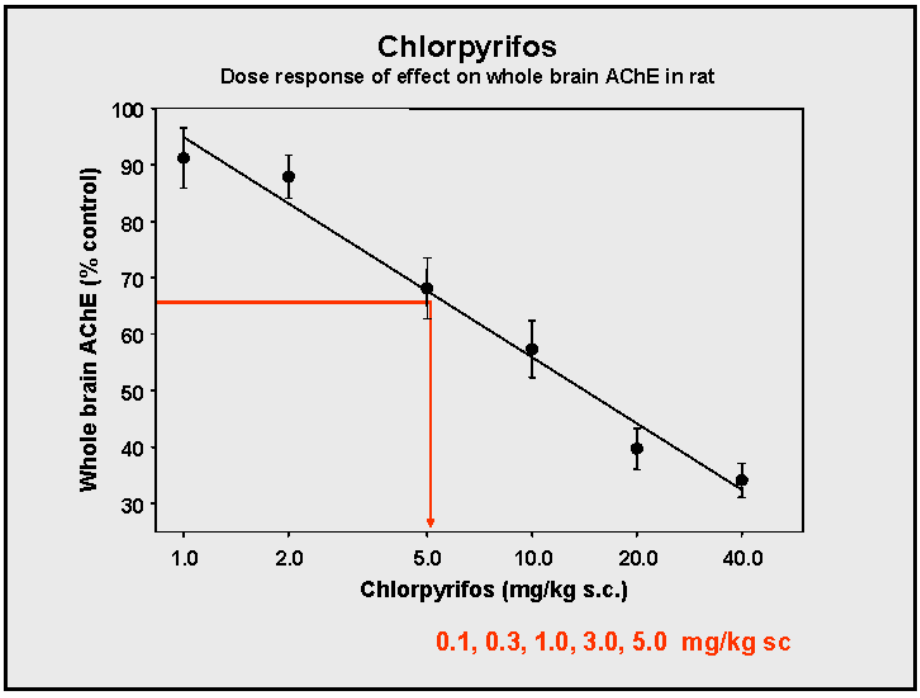
Determination of exposure parameters part 1: preliminary data in the rat

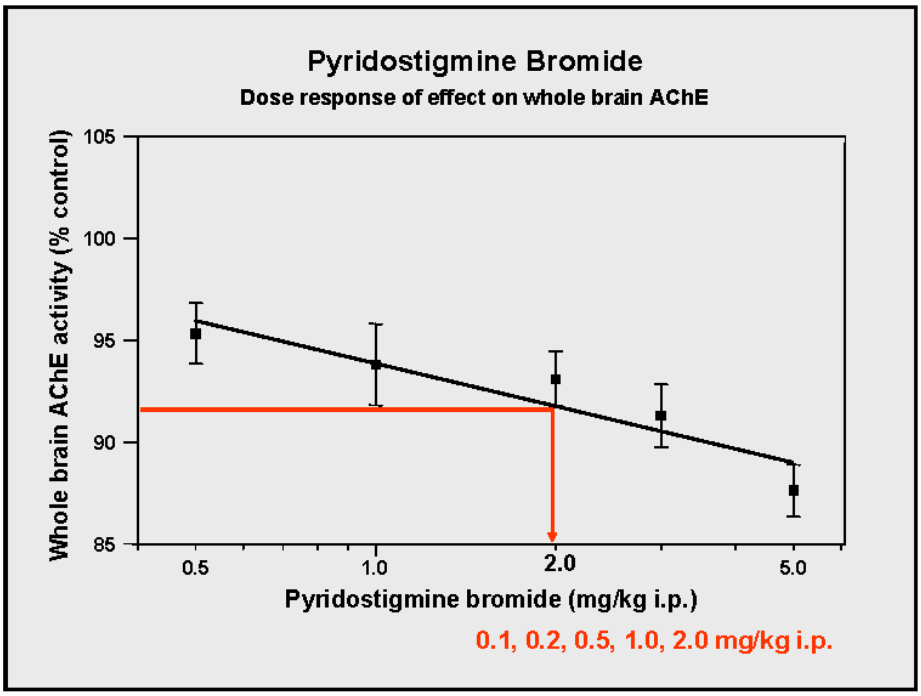
- We tested AChEi agents that were known exposure factors during the 1991 Gulf War:
  Chlorpyrifos (Dursban®), Pyridostigmine bromide (Mestinon®), DEET
- We administered the compound repeatedly:
  5 days
- We examined the delayed outcome in the whole animal using non-invasive tests sensitive to CNS function that could be applied repetitively (i.e., behavioral tests):
  3, 6 and 12 weeks
- We established a low-dose treatment regime for each compound.

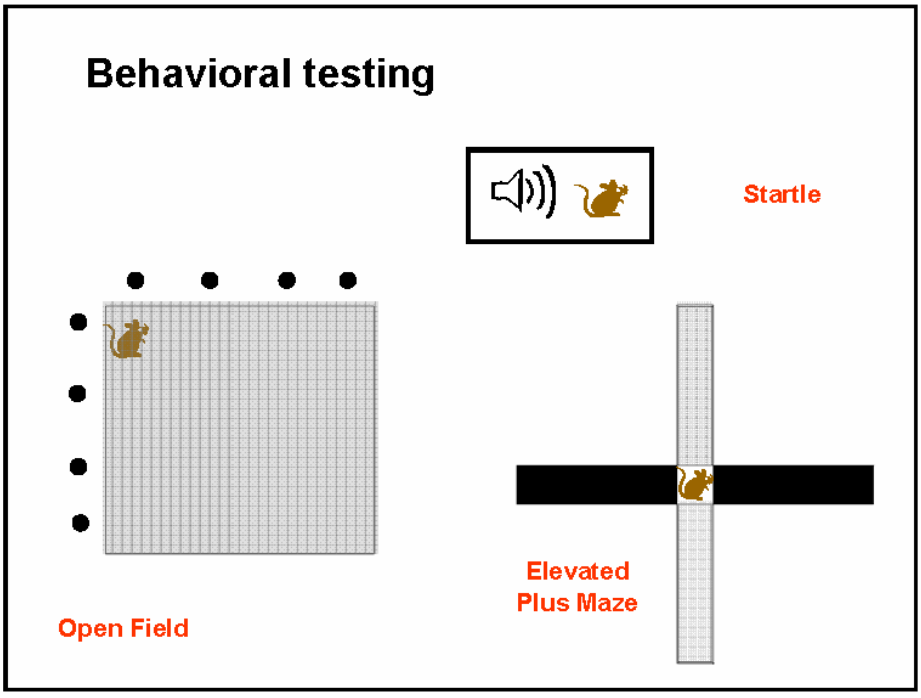


Compound treatment
Once per day for 5 days during week 0

Functional testing
Behavioral and electrophysiological tests at 3, 6 and 12 weeks after completion of compound treatment




Pyridostigmine Bromide
Dose response of effect on whole brain AChE
Whole brain AChE activity (% control)
105
100
95
90
85
0.5
1.0
2.0
5.0
Pyridostigmine bromide (mg/kg i.p.)
0.1, 0.2, 0.5, 1.0, 2.0 mg/kg i.p.


Behavioral testing
Startle
Open Field
Elevated
Plus Maze